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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,243	12/20/2005	Ghisalberti Carlo	MARGI-0044	5778

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

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02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,243	CARLO, GHISALBERTI	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 6, 8 - 20* is/are pending in the application.

4a) Of the above claim(s) *8 - 10, 15, 17, 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 6, 11 - 14, 16, 19, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 5, 2009 has been entered.

Claim Objections

2. Claim 11 is objected to because of the following informalities: the phrase "locally applying to a mammal in need thereof of a therapeutically effective amount" appears to contain an extra "of" that renders the sentence grammatical incorrect.

3. Claim 20 is objected to because of the following informalities: an extra period is present in line 3 of this claim. Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1 – 6 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Bissett et al. (WO 95/27485).

Bissett et al. discloses an emulsion composition comprising 1,2-dimethyl-3-hydroxy-pyrid-4-one (deferiprone) that is applied to twice daily to the skin (p 16, ln 8 – 29).

The claims of the instant application have an active step of topically administering a hydroxypyridonone such as deferiprone. Bissett et al. discloses topically administering the hydroxypyridonone deferiprone. Therefore, the treatment of skin microcirculatory disorders and the specific disorders listed in claim 20 must inherently be met as both the cited prior art and the instant claims recite topically administering the hydroxypyridonone deferiprone.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1 – 6, 11 – 13, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. (WO 95/24785) in view of Perricone (US 2002/0013361).

Bissett et al. discloses an emulsion composition comprising 1,2-dimethyl-3-hydroxy-pyrid-4-one (deferiprone) that is applied to twice daily to the skin (p 16, ln 8 – 29). Pharmaceutically acceptable salts of the active ingredient can also be used (p 2, ln 3 – 8). The active ingredient are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, ln 8 – 10). It is believed that the compounds bind to iron in such a way so that the iron cannot participate in the formation of radical species (p 2, ln 14 – 18).

Bissett et al. does not disclose the topical administration of the deferiprone composition to patients suffering a microcirculatory disorder such as rosacea and therefore are in need of treatment for that condition.

Perricone discloses that patients with rosacea, a chronic inflammation disorder affecting the blood vessels if the face, suffer from papule and pustules superimposed on diffuse erythema and telangiectasia (visible blood vessels) over the central portion of the face (¶ [0004]). The treatment of rosacea is the topical application of a composition comprising lipoic acid (¶ [0019]). Lipoic acid has been suggested for the treatment of inflammation and aging of the skin as because of its antioxidant activity, as it appears to prevent free radical damage (¶ [0015]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to topically apply deferiprone to a patient suffering from rosacea and/or telangiectasia. One of ordinary skill would have been motivated and reasonably would have expected success as Bissett et al. teaches that topical application of deferiprone decreases free radicals by way of iron chelation in the skin and Perricone teaches that rosacea and telangiectasia can be treated by topical application of an agent which decreases free radicals.

9. Claims 1 – 6, 11 – 14, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. and Perricone as applied to claims 1 – 6, 11 – 13, 16, 19 and 20 above, and further in view of the purpura entry from dermnet NZ (copy previously provided with Office Action mailed March 8, 2008).

Bissett et al. and Perricone teach the topical application of active ingredients which decrease free radicals in the skin for the treatment of skin conditions such as rosacea, which presents with telangiectasia (visible blood vessels). The deferiprone chelates iron and in so doing, render the iron unable to participate in the formation of free radicals.

Neither reference explicitly discloses the treatment of purpura such as actinic purpura.

Purpura is discoloration of the skin or mucus membranes caused by hemorrhage from small blood vessels as the extravasated blood breaks down and change color over time (p 1, ¶ 1). Different classifications of purpura are based on the appearance or cause of the condition, but due to overlap, there is difficulty in classifying any individual case of purpura (p 1, ¶ 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat patients suffering from various types of purpura, such as actinic purpura, itching purpura or purpura annularis telangiectodes by the topical application of deferiprone. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because deferiprone is an iron chelator which results in decreased free radicals and the treatment of skin conditions when topically applied. The various types of purpura are associated with blood, which contains large amounts of iron, escaping from blood vessels and then breaking down over time, resulting in a variety of skin colors. Given the difficulty to classifying purpura, the teaching of Bissett et al. as to the effectiveness

of topical deferiprone application to chelate iron and reduce free radicals and the teachings of Perricone that decreased free radicals in skin treat rosacea, a condition associated with visible blood vessels, one of ordinary skill in the art would reasonable expect that topical application of deferiprone to a patient suffering from a purpuric condition, characterized by leaked blood at the surface, would be treated by iron chelation and decreased free radicals caused by topical deferiprone application.

10. Claims 1 – 6, 11 – 14, 16, 19 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ghisalberti et al. (WO 01/17497) in view of Murad (US 6,630,163). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed September 5, 2008 and those set forth below.

Applicant traverses this rejection on the grounds that hemoglobin at an injection site is a side effect of the punctured blood vessel and is promptly bound by dermal and connective proteins to form hemosiderin deposits. The formation of hemosiderin deposits may stimulate the activity of the surround melanocytes. Blood fluid leakage at an injection site is not the result of the pathology caused by a microcirculatory disorder. Therefore, Ghisalberti only deals with the treatment of hyperpigmented skin which is the result of excess melanin and/or by hemosiderin deposits. Hemosiderin deposits do not arise from microcirculatory bleeding and therefore are distinct pathologies than those which are disclosed by Ghisalberti et al. Murad broadly teaches the used of fruit extracts for treating almost any dermatological disorder. Murad does not teach than an agent useful for treating hyperpigmented skin and the usefulness arises from the ant-free

radical properties of the extracts. Thus, the variety of pathologies or very different etiology can allegedly be "treated". A skilled worker would recognize that one agent cannot credibly be used to treat all of the pathologies listed. Even in the best case, Murad does not teach that a skilled worker that a particular compound normally used to treat hyperpigmentation could also be used to treat microcirculatory skin disorders.

These arguments are not found to be persuasive. Ghisalberti et al. indicates that deferiprone is an iron chelator (p 4, ln 10 – 14) and that to date, there is no treatment which treats hyperpigmentation that is the result of both excess melanin synthesis and hemosideric deposits (p 4, ln 22 – 24). Ghisalberti et al. indicates that 3-hydroxypy(id)one-derivatives, of which deferiprone is one identified member of this class, are ideal depigmenting agents as they show combined activity towards both melanin and/or hemosiderin deposits (p 5, ln 6 – 10), curing the deficiency which previously existed for the treatment of hyperpigmentation that was not casued solely by melanin.

One of ordinary skill in the art would be motivated and reasonably would expect success in the treatment of skin microcirculatory disorders by the topical application of deferiprone as it is an effective treatment agent for blood deposits outsides the vasculature system and close to the skin surface when topically applied. As discussed in greater detail in the action mailed march 4, 2008, the various types of purpura, cutaneous vasculitis and rosacea all present with blood outside of the blood vessels. Applicant has not presented any evidence to refute the cited prior art which indicates that deferiprone acts on both the hemosideric deposits - due to its ability to chelate iron

- and on the melanin deposits. Applicant has also not presented any evidence as to how blood which exits the vascular system through a puncture is treated differently by the body from blood which exits the vascular system through hemorrhage from small blood vessels like that which occurs in purpura acute vasculitis. The various skin microcirculatory disorders are all characterized by the presence of blood outside the vasculature system, which can cause hyperpigmentation as discussed by Ghisalberti et al., but can also lead to other conditions, such as purpura in its various forms or rosacea. Ghisalberti et al. teaches that 3-hydroxypy(id)one-derivatives treats hyperpigmentation which si the result of not only excess melanin pigmentation but also hemosiderin deposits.

Murad is cited to show that skin conditions with different clinical presentations and/or pathologies can be treated active ingredients which act on the common elements shared by each of the conditions. It is the common element of blood outside of the vascular system discussed above which links the various conditions together, indicating that one type of active agents can be useful in the treatment of more than one specific skin condition.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW